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(54) Title: BUCCAL FORMULATION

(57) Abstract

A buccal formulation for administering a medicament includes about 1-20% by weight of a soluble, pharmaceutically acceptable adhesive, optionally up to about 10% by weight of a pharmaceutically acceptable disintegrant and a soluble, directly compressible tablet excipient, and the medicament.

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BUCCAL FORMULATION

This application is directed to a formulation for the buccal administration of an active ingredient. Buccal administration (in the pouch of the cheek of the subject) is particularly useful for active ingredients which show poor bioavailability upon administration through other non-parenteral modes. This poor availability can be attributed to low solubility, degradation by enzyme or destruction by acid upon passing through the intestinal tract, or first-pass destruction by the liver after absorption from the gastrointestinal tract. Examples of such medicaments include: steroids such as estrogens, e.g. estradiol and derivatives such as its esters, for example the valerate, cypionate and propionate, progestins, e.g., progesterone and related compounds, androgens and anabolic steroids; propranolol; thyroid hormones; pH-sensitive peptides and small proteins such as insulin and ACTH; physostigmine; scopolamine; verapamil; and gallopamil. It is also possible to administer compounds having good oral bioavailability buccally, but normally such medicaments would be administered orally for convenience.

Buccal administration of estradiol gives an early peak in the blood level followed by decreasing concentration. This tracks the natural occurrence of

estradiol in the body, and thus is an improvement over transdermal administration, which provides a relatively constant blood level. Oral administration of estrogens such as estradiol is unpractical in view of the destruction of the active ingredient in the liver shortly after absorption from the gastrointestinal tract.

It is necessary for a buccal formulation to remain in contact with the oral mucosa for a time sufficient for absorption of the medicament that is being administered. If the formulation falls apart too quickly, the active ingredient is swallowed, and an insufficient amount of medicament is delivered. If the formulation does not fall apart quickly enough, difficulties in patient compliance can result, since the patient should not eat or drink while using the buccal formulation. The formulation should be of a small size to avoid discomfort to the patient, and it is desirable that as much of the formulation as possible be soluble in saliva so that discomfort in the form of insoluble gritty particles in the mouth can be avoided.

This invention provides a buccal composition for administration of a medicament, comprising, as essential ingredients: about 1 to about 20% by weight of a soluble, pharmaceutically acceptable polymeric adhesive; a soluble, directly compressible tablet excipient; and a therapeutically useful amount of medicament. The composition, which is in unit dosage form, may optionally contain up to about 10% (e.g., about 1 to about 10%) by weight of a pharmaceutically acceptable tablet disintegrant.

According to a further feature, this invention is directed to a buccal composition in unit dosage form for administration of an estrogen, comprising about 2 to about 10% by weight of polymeric adhesive, e.g. carbomer 934 P; up to about 6% by weight tablet disintegrant, e.g.

crospovidone; compressible sugar; and about 50 micrograms to about 2 mg of estradiol.

The buccal formulation of the present invention can also contain incidental ingredients, for example lubricants, coloring agents and flavoring agents.

The soluble, pharmaceutically acceptable polymeric adhesive is used to provide tackiness to the buccal formulation so that it will be held in place upon administration. The amount of adhesive in the formulation is about 1-20% by weight, preferably 2-10%. Use of amounts less than 1% may result in insufficient adhesive properties or the formulation falling apart too quickly, whereas excessive amounts may result in the formulation lasting for a longer period than is desirable. The adhesives desirably are sticky when moist but not when dry, for convenience in handling. The amount of adhesive which can be used generally increases with the solubility of the active ingredient.

One particularly desirable group of polymeric adhesives is high molecular weight polymers of acrylic acid known as carbomers. Molecular weights of 450,000 to 4,000,000 are particularly useful, especially about 3,000,000 (e.g., as for carbomer 934 P). These substances are sold by B.F. Goodrich under the trademark Carbopol . These adhesives have been found to allow use of very small amounts to provide the desired adhesive characteristics to the formulation, which is advantageous since large amounts of adhesive may impede the dissolution of the active ingredient. Other suitable hydrophilic polymers usable as polymeric adhesives include partially (e.g. 87-89%) hydrolyzed polyvinylalcohol (molecular weight 10,000 to 125,000, preferably 11,000 to 31,000), polyethylene oxide (molecular weight about 100,000 to about 5,000,000, preferably about 400,000) and polyacrylates, such as that

sold by GAF under the trademark Gantrez , particularly those designated as high molecular weight polyacrylates. Hydroxypropyl methylcellulose, having a molecular weight of 13,000 to 140,000 (sold under the trademark Methocel by Dow), and hydroxypropyl cellulose, having a molecular weight of 60,000 to 1,000,000 (sold under the trademark Klucel) also are useful adhesives. Material toward the high end of each of the molecular weight ranges is preferred. The term "soluble" is used throughout this application as an indication that the material is soluble in water or saliva.

Upon administration of the formulation, the adhesive therein forms a gel-like substance which is gradually broken up. Use of a small amount of a pharmaceutically acceptable disintegrant that swells upon administration, thus exposing more of the formulation to saliva, can aid this break-up and cause the formulation to break up gradually. The amount of disintegrant in the formulation is up to 10% by weight, e.g., 3-6%. However, excessive amounts of disintegrant actually may unduly delay disintegration, as by formation of an insoluble gel, instead of aiding dissolution of the formulation by expansion. Indeed, some formulations of this type may show faster disintegration if less than 3%, e.g., 2.5%, or even only 1% or less, disintegrant is used, especially where the disintegrant is substantially non-wettable by water or sparingly soluble in water; such a disintegrant indeed by inhibiting entry of water into the composition can unduly delay its disintegration and dissolution. The selection of the right amount of disintegrant can nonetheless be found by trial and error. Some formulations may lack disintegrant altogether or contain only a very small percentage, e.g. 0.05% or 0.1% to 0.9%.

One useful disintegrant is the material crospovidone, which is a cross-linked polyvinyl-

pyrrolidone product. This material is sold under the trademark Polyplasdone XL by GAF. Other useful disintegrants include Ac-di-sol (FMC's trademark for croscarmellose, a cross-linked carboxymethylcellulose), alginic acid and sodium carboxymethyl starch such as that sold as Explotab by Edward Mendell Co., Inc.

The formulation also includes a soluble, directly compressible tableting excipient such as a sugar. One such useful tableting excipient is a co-crystallization of 97% sucrose and 3% highly modified dextrins sold under the trademark Di-Pac by Amstar. Other such excipients known to those skilled in the art, such as lactose, also may be used. The amount of excipient used is such that the resulting formulation is big enough to be handled conveniently, yet small enough to dissolve properly. Other ingredients which may be used include lubricants, coloring agents and flavoring agents. The lubricant may be water-insoluble, e.g. magnesium stearate or oleate, conveniently in an amount of up to 3.0% by weight, preferably 0.3% to 1.5%. However, a preferred lubricant is water-soluble, e.g. sodium lauryl sulfate, conveniently in an amount of up to 3.0% by weight, preferably 0.3% to 1.5%. A mixture of water-soluble and water-insoluble lubricants can be used. A soluble lubricant may tend to shorten disintegration and dissolution times, especially for a water-insoluble medicament, whereas an insoluble lubricant may tend to lengthen them.

Active ingredients useful with this invention include those mentioned in the first paragraph of this specification. Of course, the amount will vary depending upon the dosage desired for a given treatment. Estradiol, when used as the active ingredient, is conveniently present in the amount of about 50 micrograms to about 2 mg.

The formulations of the present invention can be prepared by simply mixing the ingredients together and compressing desired amounts of the mixture into tablet form. The final formulations desirably have a diameter of about 0.635 cm (about a quarter inch) and a thickness of about 0.127 cm (about 0.05 inches), and upon administration disintegrate in about 2-20 minutes, preferably about 4-12 minutes.

The present invention is illustrated by the following non-limiting examples.

EXAMPLE 1

The following ingredients are charged into a blender and mixed for ten minutes.

% BY WEIGHT	INGREDIENT	AMOUNT
0.2	Estradiol, USP (Micronized)	2.0 g
89.3	Di-Pac (Compressible Sugar, NF)	893.0 g
5.0	Carbomer 934P, NF (Carbopol 934P)	50.0 g
5.0	Crospovidone, NF (Polyplasdone XL)	50.0 g
0.5	Magnesium Stearate, NF	5.0 g
100.0		1,000.0 g

Tablets weighing about 0.05 gm. each are formed using a compression force of about 6,900 kPa (about 1000 PSI). The batch yields about 20,000 tablets which upon

administration disintegrate in about 10-15 minutes. The tablets are about 0.635 cm (about a quarter inch) in diameter.

EXAMPLE 2

Following the procedure of Example 1, the following are mixed and formed into tablets:

% BY WEIGHT	INGREDIENT	AMOUNT
0.4	Estradiol, USP (Micronized)	4.0 g
89.0	Di-Pac (Compressible Sugar, NF)	890.0 g
5.0	Carbomer 934P, NF (Carbopol 934P)	50.0 g
5.0	Crospovidone, NF (Polyplasdone XL)	50.0 g
0.5	Magnesium Stearate, NF	5.0 g
0.1	FDC Yellow #6 Lake	1.0 g
100.0		1,000.0 g

Results similar to those of Example 1 are obtained.

EXAMPLE 3

Following the procedure of Example 1, the following are mixed and formed into tablets:

% BY WEIGHT	INGREDIENT	AMOUNT
0.2	Estradiol, USP (Micronized)	2.0 g
96.3	Di-Pac (Compressible Sugar, NF)	963.0 g
2.5	Carbomer 934P, NF (Carbopol 934P)	25.0 g
1.0	Sodium lauryl sulfate NF	10.0 g
100.0		1,000.0 g

These tablets disintegrate in about 3 to 3-and-a-half minutes, but dissolution is complete only after about 45 minutes.

EXAMPLE 4

Following the procedure of Example 1, the following are mixed and formed into tablets:

% BY WEIGHT	INGREDIENT	AMOUNT
0.2	Estradiol, USP (Micronized)	2.0 g
96.2	Di-Pac (Compressible Sugar, NF)	962.0 g

2.5	Carbomer 934P, NF (Carbopol 934P)	25.0 g
0.1	Crospovidone, NF (Polyplasdone XL)	1.0 g
1.0	Sodium lauryl sulfate, NF	10.0 g
100.0		1,000.0 g

EXAMPLE 5

Following the procedure of Example 1, the following are mixed and formed into tablets:

% BY WEIGHT	INGREDIENT	AMOUNT
0.2	Estradiol, USP (Micronized)	2.0 g
95.4	Di-Pac (Compressible Sugar, NF)	954.0 g
2.5	Carbomer 934P, NF (Carbopol 934P)	25.0 g
0.9	Crospovidone, NF (Polyplasdone XL)	9.0 g
1.0	Sodium lauryl sulfate, NF	10.0 g
100.0		1,000.0 g

The estradiol used in the above Examples can be replaced with appropriate amounts of other active ingredients, e.g., those mentioned in the first paragraph of this specification, with appropriate adjustment of the amount of other ingredients, especially of the compressible sugar.

CLAIMS:

1. A buccal composition for administration of an active ingredient comprising as essential ingredients:

(a) about 1 to about 20% by weight of a soluble, pharmaceutically acceptable polymeric adhesive;

(b) a soluble, directly compressible tablet excipient; and

(c) a therapeutically useful amount of active ingredient.

2. A composition as claimed in claim 1, wherein said adhesive, which is preferaby present in an amount of about 2 to about 10% by weight, is partially hydrolyzed polyvinyl alcohol, polyethylene oxide, polyacrylate, hydroxypropyl methylcellulose or hydroxypropyl cellulose, or especialy a carbomer, in particular carbomer 934P.

3. A composition as claimed in claim 1 or claim 2 wherein said excipient is a compressible sugar.

4. A composition as claimed in any of claims 1 to 3 wherein said active ingredient is a progestin, an androgen, an anabolic steroid, propranolol, insulin, ACTH, physostigmine, scopolamine, verapamil, or gallopamil, or especialy an estrogen, in particular estradiol or a pharmaceutically acceptable derivative thereof, which is preferably present in an amount of about 50 micrograms to about 2 mg.

5. A composition as claimed in any of claims 1 to 4 further comprising up to about 10% by weight, e.g., about

3 to about 6% by weight, of a pharmaceutically acceptable tablet disintegrant.

6. A composition as claimed in claim 4 wherein said disintegrant is cross-linked polyvinylpyrrolidone, cross-linked carboxymethylcellulose, alginic acid or sodium carboxymethyl starch, especially crospovidone.

7. A composition as claimed in claim 5 or claim 6 wherein the amount of disintegrant is less than 1% by weight.

8. A buccal composition as claimed in claim 1 for unit dosage administration of an estrogen, comprising:

(a) about 2 to about 10% by weight of carbomer 934P;

(b) about 3 to about 6% by weight crospovidone;

(c) compressible sugar; and

(d) a therapeutically useful amount of an estrogen.

9. A buccal composition as claimed in claim 1 for unit dosage administration of an estrogen, comprising:

(a) about 2 to about 10% by weight of carbomer 934P;

(b) less than 1% by weight crospovidone;

(c) compressible sugar; and

(d) a therapeutically useful amount of an estrogen.

10. A composition as claimed in claim 8 or claim 9 wherein the estrogen is estradiol in the amount of about 50 micrograms to about 2 mg. per unit dose.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 87/00031

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 9/20

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	US, A, 3033754 (KRAHNKE et al.) 8 May 1962 see the whole document	1,2
X	FR, A, 2285896 (NIPPON KAYAKU K.K.) 23 April 1976, see page 1, lines 1-39; page 2, line 18 - page 5, line 36; claims 1,2,4,6-8,10	1-4
X	EP, A, 0095944 (TAKEDA CHEMICAL INDUSTRIES) 7 December 1983, see page 2, lines 1-15; page 4, line 34 - page 7, line 22; page 8, table 2, example E; page 11, example 5	1-4
Y		5-10
Y	Journal of Pharmaceutical Sciences, volume 62, no. 1, January 1973, (Washington, US), S.S. Kornblum et al.: "A new table disintegrating agent: cross-linked polyvinylpyrrolidone", pages 43-49, see page 45, table 1	5-10

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
30th March 1987	29 APR 1987
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INTERNATIONAL APPLICATION NO. PCT/US 87/00031 (SA 15875)

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 3033754		None		
FR-A- 2285896	23/04/76	DE-A,C	2542158	01/04/76
		US-A-	4059686	22/11/77
		JP-A-	51038412	31/03/76
EP-A- 0095944	07/12/83	JP-A-	58210007	07/12/83

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